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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/661,097

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Andrew Vaillant

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EXAMINER

ZARA, JANE J

ART UNIT

PAPER NUMBER

1635

MAIL DATE

DELIVERY MODE

03/06/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/661,097	Applicant(s) VAILLANT ET AL.	
	Examiner Jane Zara	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 August 2007 and 20 December 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,14,15,17,18,21,22,27-29 and 39-42 is/are pending in the application.
- 4a) Of the above claim(s) 40 and 41 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 14, 15, 17, 18, 21, 22, 27-29, 39 and 42 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>7-24-07</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This Office action is in response to the communications filed 8-14-07 and 12-20-07.

Claims 1, 2, 14, 15, 17, 18, 21, 22, 27-29, 39-42 are pending in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8-14-07 has been entered.

Election/Restrictions

Applicant's election with traverse of SEQ ID NO. 24, claims 1, 2, 14, 15, 17, 18, 21, 22, 27-29, 39 and 42 in the reply filed on 12-20-07 is acknowledged. The traversal is on the ground(s) that the sequences should not be restricted because they are all randomers, and, although they specifically recite particular SEQ ID NOs, their mode of action is non-complementarity. This is not found persuasive because each sequence is chemically and structurally distinct from the other, and the searches of the necessary data bases, both non-patent and patent data bases, that would be required for properly

examining all of the oligonucleotides claimed, would pose a serious search burden on the PTO and the examiner.

The requirement is still deemed proper and is therefore made FINAL.

Claims 40, 41 and SEQ ID NOs. other than SEQ ID NO. 24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 12-20-07.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 1, 2, 14, 15, 17, 18, 21, 22, 27-29 and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record set forth in the Office action mailed 12-19-06.

Applicant's arguments filed 8-14-07 have been fully considered but they are not persuasive. Applicant argues that adequate description has been provided for the broad genus of compounds claimed.

Applicant argues that the three species of oligonucleotides disclosed in the instant specification, and two oligonucleotides provided in the Declaration filed October 5, 2006, some of which were found to provide treatment and prophylactic effects in an appropriate animal model, provide adequate description for the very large genus

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comprising any oligonucleotide at least 30 nucleotides in length which provides anti-viral activity by a “non-sequence complementary mode of action,” and which is “non-sequence complementary” (e.g., to a viral gene).

The claims are drawn to methods for the prophylaxis or treatment of HSV-1, HSV-2 and CMV infection in a subject comprising the administration of any oligonucleotide at least 30 nucleotides in length, which is optionally double or single-stranded, which provides anti-viral activity by a non-sequence complementary mode of action, and which is non-sequence complementary, and which optionally comprises at least a portion of a sequence from a viral genome, and which oligonucleotide further comprises at least one phosphorothioated linkage.

The specification and claims do not adequately describe the distinguishing features or attributes concisely shared by the members of the genus comprising oligonucleotides with “non-sequence complementary” modes of action and comprising any random sequences, whereby prevention and treatment of HSV-1, HSV-2 or CMV is obtained in an organism. It is unclear what is embraced by anti-viral activity occurring principally by a “non-sequence complementary mode of action.” This can involve various modes of actions, including, but not limited to aptamers or dendrimer-like molecules that interfere with mature capsid formation, or aptamers that inhibit some other vital viral maturation pathway.

The specification teaches rather large differences in the abilities of various randomers to inhibit different viral infections, and each randomer is tested empirically because no concise description of common characteristics for this expansive genus has

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been provided. The disclosure of five effective oligonucleotides found to reduce or prevent viral infectivity of some strains of virus, with no common features, physical characteristics, or modes of action described or purportedly shared between them, do not provide adequate description for the very large genus of oligonucleotides claimed.

The instant disclosure and declaration filed October 5, 2006 do not clarify what common attributes, if any, are encompassed by this very broad genus. Concise structural features that would distinguish structures within the broadly claimed genus from those outside the genus, are missing from the disclosure, and without empirically testing each candidate oligomer, it is unclear which of these species would provide for the functions claimed, the ability to prevent or inhibit viral infections, including the instantly claimed HSV-1, HSV-2 and/or CMV infections in a subject.

For these reasons, the very broad large genus claimed was not adequately described at the time of filing by Applicant.

Claims 1, 2, 14, 15, 17, 18, 21, 22, 27-29 and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons of record set forth in the Office action mailed 12-19-06.

Applicant's arguments filed 8-14-07 have been fully considered but they are not persuasive. Applicant argues the full scope of invention is enabled.

Applicant argues that the three species of oligonucleotides disclosed in the instant specification, and two oligonucleotides provided in the Declaration filed October 5, 2006, which were found to provide treatment and prophylactic effects in an

appropriate animal model, indeed provide adequate description for the very large genus comprising any oligonucleotide at least 30 nucleotides in length which provides anti-viral activity by a “non-sequence complementary mode of action,” and which is “non-sequence complementary” (e.g., to a viral gene).

Applicant argues that the full scope of the claims is enabled because the instant disclosure, at examples 2 and figure 15, disclose various oligonucleotides with different lengths used to identify their efficacy as potential anti- HSV-2 molecules. In addition, according to Applicant, in vivo efficacy has been shown for three oligonucleotides - two oligonucleotides (REP 2006 and 2031) were found to prevent HSV-2 transmission in a mouse model, and three oligonucleotides (REP 2006, 2031 and 2107) reduced CMV liver titers upon intraperitoneal administration in a mouse model.

The specification teaches the in vitro inhibition of HSV-2 using oligonucleotides which are partially complementary to a target HSV-2 gene sequence. These experiments, however, are not representative of providing in vivo treatment or prophylaxis using a representative number of species of the expansive genus of nucleic acid molecules claimed.

Applicant is correct that in vivo efficacy has been shown for the particularly described oligonucleotides, REP 2006, 2031 and 2107, regarding their ability to prevent or reduce HSV-2 or CMV infections in appropriate animal models as indicated in the declaration. The instant application therefore appears to be enabled for the ability to treat CMV upon systemic administration of REP 2006, 2031 and 2107, and for the ability to treat or prevent HSV-2 infection upon administration of REP 2006 and 2031.

The full scope of the claims, however, drawn to methods for the prevention and treatment of HSV-1, -2, and CMV comprising administration of any (random) oligonucleotide at least 30 nucleotides in length with anti-viral activity occurring by any non-sequence complementary mode of action, is not enabled.

The ability to predict a particular randomer's ability to treat or prevent a viral infection in a subject is a highly unpredictable endeavor. The ability of three oligonucleotides to provide treatment effects of CMV and of two oligonucleotides to provide treatment or prophylactic effects for HSV-2 is not correlative or representative of the ability to predict the efficacy of any oligonucleotide of at least 30 nucleotides and with at least one phosphorothioate, acting in any non-complementary mode, to provide such prophylactic effects in a subject. This requires experimentation beyond that provided in the instant specification.

For these reasons, the instant rejection is maintained.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 29 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 29, lines 2-3, recites the limitation that "at least a portion" of the claimed oligonucleotide is derived from a viral genome. The metes and bounds of "at least a portion" cannot be determined.

It is also unclear whether the "viral genome" in claim 29, line 3 refers to the particular viruses recited in claim 1 (from which claim 29 depends) or instead refer to any viral genome.

Appropriate clarification is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 14, 15, 17, 18, 21, 22, 27-29, 39 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sundquist et al (US 2005/0009743) in view of

Trus et al (J. Mol. Biol., Vol. 263, pages 447-462, 1996) and McKay et al (USPN 6,133,246) insofar as the claims are drawn to a method for treatment of HSV-1, HSV-2 or CMV infection in a subject comprising the administration of SEQ ID NO. 24, which provides anti-viral activity by a non-sequence complementary mode of action, and which further comprises at least one phosphorothioated linkage, and optionally further comprises 2'-O-modified sugars, a methylphosphonate linkage.

Sundquist et al (US 2005/0009743) teach SEQ ID NO. 24 for inhibiting viral assembly by interfering with requisite conformational changes that must occur in capsid formation, and teach approaches to inhibit capsid maturation, and hence inhibit viral replication (see esp. paragraph 0003, pages 6-7, paragraphs 0088-0089, 01080184-0192, and SEQ ID NO. 28 of Sundquist et al).

Sundquist does not teach inhibition of HSV or CMV using SEQ ID NO. 24, nor the incorporation of modified internucleotide linkages (phosphorothioates), methyl phosphonates or 2'-O-sugar modifications into the oligonucleotide.

Trus et al (J. Mol. Biol., Vol. 263, pages 447-462, 1996) the importance of correct prohead assembly in viral capsid formation in HSV, and the conformational changes associated with capsid formation that are critical for viral maturation, viral particle formation and viral infectivity. (see the abstract on p. 447, text in right hand col. on p. 448, fig. 3 on p. 451, right hand col. on p. 458).

McKay et al (USPN 6,133,246) teach the incorporation of phosphorothioates, methyl phosphonates and 2'-O-sugar modifications for enhancing oligonucleotide stability (see esp. col. 9-10).

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It would have been obvious to one of ordinary skill in the art to utilize the oligonucleotide of SEQ ID NO. 24 for inhibiting capsid formation in a virus because Sundquist teaches SEQ ID NO. 24 for inhibiting viral assembly by interfering with capsid formation of a virus. One would have been motivated to test the previously identified SE ID No. 24 for its ability to inhibit capsid formation in other viruses, because both Sundquist and Trus teach the necessity of structural changes in capsid maturation in various viruses, and the vulnerability of viruses in disrupting this process, including in HIV and HSV maturation.

One of ordinary skill in the art would have been motivated to incorporate the well known modifications of phosphorothioates, methyl phosphonates and 2'-O-sugar modifications into oligonucleotides because the technology to do so was well known in the art at the time of the instant invention, and McKay teaches the advantages of incorporating these modifications into oligonucleotides for enhancing binding properties and oligonucleotide stability.

One of ordinary skill in the art would have reasonably expected that the oligonucleotide previously identified by Sundquist as an inhibitor of viral capsid formation in HIV would interfere with capsid formation in other viruses because the general vulnerability of viruses in interfering with their capsid formation was well known in the art at the time the invention was made, and the interference with hydrophobic interactions during capsid maturation was also well documented in the art for different types of viruses, as taught previously by both Sundquist and Trus. One of ordinary skill in the art would have been motivated to test what was identified as an inhibitor of capsid

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formation in one virus as a potential inhibitor in another virus, because both HIV and HSV require proper capsid formation for their replication, and both are involved in deleterious effects when they infect humans.

For these reasons, the instant invention would have been obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

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published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
2-26-08

/Jane Zara/

Primary Examiner, Art Unit 1635